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TIBBETTER OSIGI

CLAIMS

1. A compound of the formula 1

$$R^{4}$$
 $R^{1}$ 
 $R^{1$ 

or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein: m is an integer from 0 to 3;

p is an integer from 0 to 4

each R1 and R2 is independently selected from H and C1-C6 alkyl;

 $R^3$  is -( $CR^1R^2$ )<sub>i</sub>(4 to 10 membered heterocyclic), wherein t is an integer from 0 to 5, said heterocyclic group is optionally fused to a benzene ring or a  $C_5$ - $C_8$  cycloalkyl group, the -( $CR^1R^2$ )<sub>i</sub>- moiety of the foregoing  $R^3$  group optionally includes a carbon-carbon double or triple bond where t is an integer between 2 and 5, and the foregoing  $R^3$  groups, including any optional fused rings referred to above, are optionally substituted by 1 to 5  $R^8$  groups;

 $R^4$  is  $-(CR^{16}R^{17})_m$ - $C=C-(CR^{16}R^{17})_tR^9$ ,  $-(CR^{16}R^{17})_m$ - $C=C-(CR^{16}R^{17})_t-R^9$ ,  $-(CR^{16}R^{17})_m$ - $C=C-(CR^{16}R^{17})_kR^{13}$ , or  $-(CR^{16}R^{17})_tR^9$ , wherein the attachment point to  $R^9$  is through a carbon atom of the  $R^9$  group, each k is an integer from 1 to 3, each t is an integer from 0 to 5, and each m is an integer from 0 to 3;

each  $R^5$  is independently selected from halo, hydroxy, -NR<sup>1</sup>R<sup>2</sup>, C<sub>1</sub>-C<sub>6</sub> alkyl, trifluoromethyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, trifluoromethoxy, -NR<sup>6</sup>C(O)R<sup>1</sup>, -C(O)NR<sup>6</sup>R<sup>7</sup>, -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>C(O)NR<sup>7</sup>R<sup>1</sup>, and -NR<sup>6</sup>C(O)OR<sup>7</sup>;

each  $R^6$ ,  $R^{6a}$  and  $R^7$  is independently selected from H,  $C_1$ - $C_6$  alkyl, -( $C_8$ - $C_{10}$  aryl), and -( $C_8$ - $C_{10}$ ), (4 to 10 membered heterocyclic), wherein t is an integer from 0 to 5, 1 or 2 ring carbon atoms of the heterocyclic group are optionally substituted with an oxo (=O) moiety, the alkyl, aryl and heterocyclic moieties of the foregoing  $R^6$  and  $R^7$  groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, -NR $^1$ R $^2$ , trifluoromethyl, trifluoromethoxy,  $C_1$ - $C_6$  alkyl,  $C_2$ - $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl, hydroxy, and  $C_1$ - $C_6$  alkoxy;

or R<sup>6</sup> and R<sup>7</sup>, or R<sup>6a</sup> and R<sup>7</sup>, when attached to the same nitrogen atom, can be taken together to form a 4 to 10 membered heterocyclic ring which may include 1 to 3 additional

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hetero moieties, in addition to the nitrogen to which said R6, R6a, and R7 are attached, selected from N, N(R1), O, and S, provided two O atoms, two S atoms or an O and S atom are not attached directly to each other;

each R<sup>8</sup> is independently selected from oxo (=O), halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>10</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl,  $-C(O)R^6$ ,  $-C(O)R^6$ ,  $-OC(O)R^6$ ,  $-NR^6C(O)R^7$ ,  $-NR^6SO_2NR^7R^1$ ,  $-NR^6C(O)NR^1R^7$ ,  $-NR^6C(O)OR^7$ , -C(O)NR<sup>6</sup>R<sup>7</sup>, -NR<sup>6</sup>OR<sup>7</sup>, -SO<sub>2</sub>NR<sup>6</sup>R<sup>7</sup>, -S(O)<sub>i</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl) wherein j is an integer from 0 -(CR1R3),(C6-C10 -(CR<sup>1</sup>R<sup>2</sup>)<sub>t</sub>(4 to heterocyclic), aryl), 10 membered  $-(CR^{1}R^{2})_{q}C(O)(CR^{1}R^{2})_{t}(C_{6}-C_{10} \text{ aryl}), \ -(CR^{1}R^{2})_{q}C(O)(CR^{1}R^{2})_{t}(4 \text{ to } 10 \text{ membered heterocyclic}),$  $-(CR^1R^2)_1O(CR^1R^2)_q(C_6C_{10}$  aryl),  $-(CR^1R^2)_1O(CR^1R^2)_q(4$  to 10 membered heterocyclic),  $-(CR^1R^2)_qS(O)_i(CR^1R^2)_i(C_{0i}^2C_{10} \text{ aryl}), \text{ and } -(CR^1R^2)_qS(O)_i(CR^1R^2)_i(4 \text{ to } 10 \text{ membered})$ heterocyclic), wherein j is 0,1 or 2, q and t are each independently an integer from 0 to 5, 1 or 2 ring carbon atoms of the heterocyclic moieties of the foregoing R8 groups are optionally substituted with an oxo (=O) moiety, and the alkyl, alkenyl, alkynyl, aryl and heterocyclic moieties of the foregoing R8 groups are optionally substituted with 1 to 3 substituents independently selected from halo, cyano, nitro, trifluoromethyl, trifluoromethoxy, azido, -OR6,  $-C(O)R^6$ ,  $-C(O)OR^6$ ,  $-OC(O)R^6$ ,  $-NR^6C(O)R^7$ ,  $-C(O)NR^6R^7$ ,  $-NR^6R^7$ ,  $-NR^6OR^7$ ,  $C_1-C_6$  alkyl,  $C_2-C_6$  $C_6$  alkenyl,  $C_2$ - $C_6$  alkynyl, -( $CR^1R^2$ ),  $C_6$ - $C_{10}$  aryl), and -( $CR^1R^2$ ), (4 to 10 membered heterocyclic), wherein t is an integer from 0 to 5;

R9 is a non-aromatic mono-cyclic ring, a fused or bridged bicyclic ring, or a spirocyclic ring, wherein said ring contains from 3 to 12 carbon atoms in which from 0 to 3 carbon atoms are optionally replaced with a hetero moiety independently selected from N, O, S(O), wherein j is an integer from 0 to 2, and -NR1-, provided that two O atoms, two S(O), moieties, an O atom and a S(O)<sub>j</sub> moiety, an N atom and an S atom, or an N atom and an O atom are not attached directly to each other within said ring, and wherein the carbon atoms of said ring are optionally substituted with 1 or 2 R8 groups;

each R11 is independently selected from the substituents provided in the definition of R8, except R11 is not oxo(=O);

 $R^{12}$  is  $R^6$ ,  $-OR^6$ ,  $-OC(O)R^6$ ,  $-OC(O)NR^6R^7$ ,  $-OCO_2R^6$ ,  $-S(O)_iR^6$ ,  $-S(O)_iNR^6R^7$ ,  $-NR^6R^7$ ,  $-NR^6C(O)R^7, -NR^6SO_2R^7, -NR^6C(O)NR^{6a}R^7, -NR^6SO_2NR^{6a}R^7, -NR^6CO_2R^7, CN, -C(O)R^6, or the context of the cont$ halo, wherein j is an integer from 0 to 2;

R<sup>13</sup> is -NR<sup>1</sup>R<sup>14</sup> or -OR<sup>14</sup>:

 $R^{14}$  is H,  $R^{15}$ ,  $-C(O)R^{15}$ ,  $-SO_2R^{15}$ ,  $-C(O)NR^{15}R^7$ ,  $-SO_2NR^{15}R^7$ , or  $-CO_2R^{15}$ ;

 $R^{15}$  is  $R^{18}$ , -( $CR^1R^2$ ),( $C_6$ - $C_{10}$  aryl), -( $CR^1R^2$ ),(4 to 10 membered heterocyclic), wherein t is an integer from 0 to 5, 1 or 2 ring carbon atoms of the heterocyclic group are optionally

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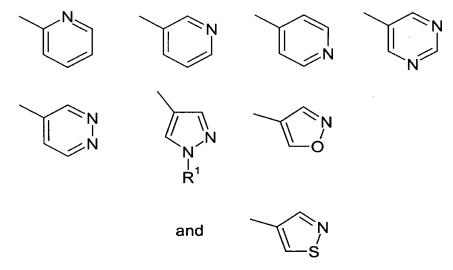
substituted with an oxo (=O) moiety, and the aryl and heterocyclic moieties of the foregoing R<sup>15</sup> groups are optionally substituted with 1 to 3 R<sup>8</sup> substituents;

each  $R^{16}$  and  $R^{17}$  is independently selected from H,  $C_1$ - $C_6$  alkyl, and  $-CH_2OH$ , or  $R^{16}$  and R<sup>17</sup> are taken together as -CH<sub>2</sub>CH<sub>2</sub>- or -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-;

R18 is C1-C6 alkyl wherein each carbon not bound to a N or O atom, or to S(O), wherein j is an integer from 0 to 2, is optionally substituted with  $R^{12}$ ;

and wherein any of the above-mentioned substituents comprising a CH<sub>3</sub> (methyl), CH<sub>2</sub> (methylene), or CH (methine) group, which is not attached to a halogeno, SO or SO2 group or to a N, O or S atom, is optionally substituted with a group selected from hydroxy, halo, C1-C4 alkyl, C1-C4 alkoxy and -NR1R2.

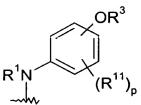
- 2. A compound according to claim 1 wherein R3 is -(CR1R2),(4 to 10 membered heterocyclic), wherein t is an integer from 0 to 5; said heterocyclic group is optionally fused to a benzene ring or a C5-C8 cycloalkyl group, and the foregoing R3 groups, including any optional fused rings referred to above, are optionally substituted by 1 to 3 R<sup>8</sup> groups.
- 3. A compound according to claim 1 wherein R3 is -(CR1R2),(4 to 10 membered heterocyclic), wherein t is an integer from 0 to 5, and the foregoing R3 groups are optionally substituted by 1 to 3 R8 groups.
  - 4. A compound according to claim 1 wherein R3 is selected from



wherein the foregoing R<sup>3</sup> groups are optionally substituted by 1 to 3 R<sup>8</sup> groups.

- 5. A compound according to claim 1 wherein R3 is pyridin-3-yl optionally substituted by 1 to 3 R8 groups.
- 6. A compound according to claim 1 wherein the following structural portion of the compound of formula 1





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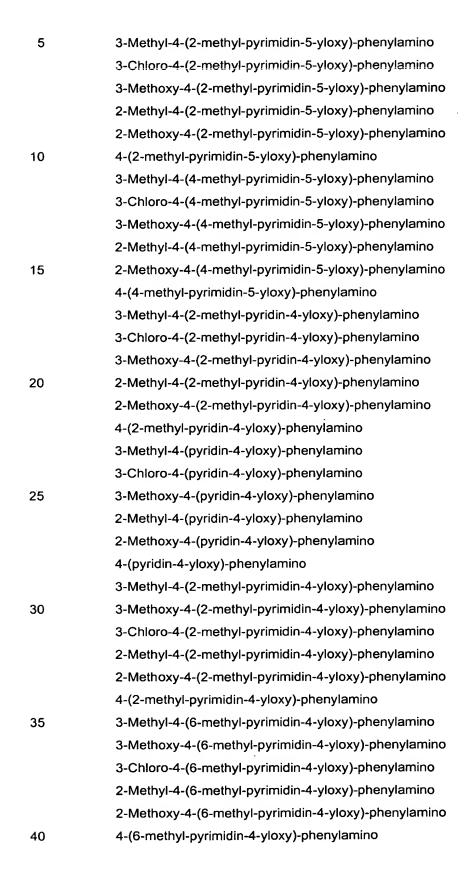
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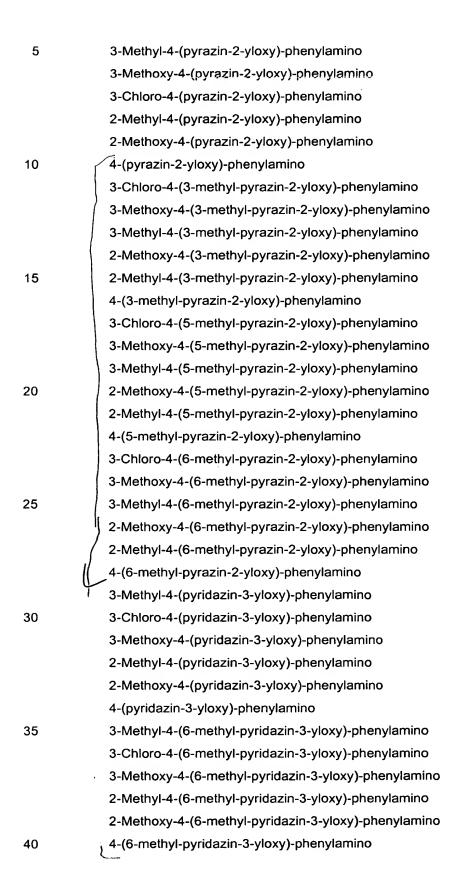
is selected from the group consisting of 3-Methyl-4-(pyridin-2-yloxy)-phenylamino 3-Chloro-4-(pyridin-2-yloxy)-phenylamino 3-Methoxy-4-(pyridin-2-yloxy)-phenylamino 4-(pyridin-2-yloxy)-phenylamino 2-Methyl-4-(pyridin-2-yloxy)-phenylamino 2-Methoxy-4-(pyridin-2-yloxy)-phenylamine 3-Chloro-4-(6-methyl-pyridin-2-yloxy)-phenylamino 3-Methoxy-4-(6-methyl-pyridin-2-yloxy)-phenylamino 3-Methyl-4-(6-methyl-pyridin-2-yloxy)-phenylamino 2-Methoxy-4-(6-methyl-pyridin-2-yloxy)-phenylamino 2-Methyl-4-(6-methyl-pyridin-2-yloxy)-phenylamino 4-(6-methyl-pyridin-2-yloxy)-phenylamino 3-Methoxy-4-(2-methyl-pyridin-3-yloxy)-phenylamino 3-Methyl-4-(2-methyl-pyridin-3-yloxy)-phenylamino 3-Chloro-4-(2-methyl-pyridin-3-yloxy)-phenylamino 2-Methoxy-4-(2-methyl-pyridin-3-yloxy)-phenylamino 2-Methyl-4-(2-methyl-pyridin-3-yloxy)-phenylamino 4-(2-methyl-pyridin-3-yloxy)-phenylamino 3-Methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino 3-Chloro-4-(6-methyl-pyridin-3-yloxy)-phenylamino 3-Methoxy-4-(6-methyl-pyridin-3-yloxy)-phenylamino 2-Methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino 2-Methoxy-4-(6-methyl-pyridin-3-yloxy)-phenylamino 4-(6-methyl-pyridin-3-yloxy)-phenylamino 3-Methyl-4-(pyridin-3-yloxy)-phenylamino 3-Chloro-4-(pyridin-3-yloxy)-phenylamino 3-Methoxy-4-(pyridin-3-yloxy)-phenylamino

2-Methyl-4-(pyridin-3-yloxy)-phenylamino

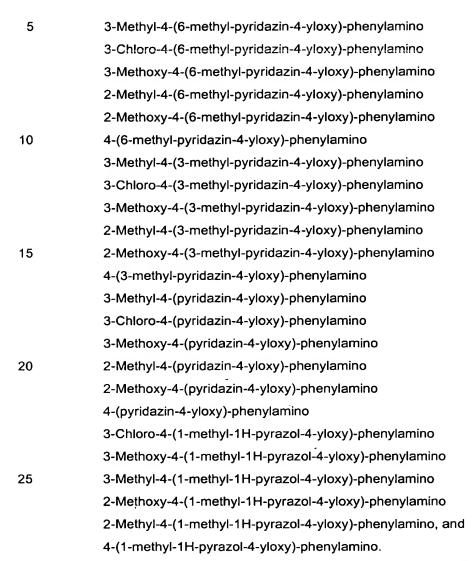
4-(pyridin-3-yloxy)-phenylamino

2-Methoxy-4-(pyridin-3-yloxy)-phenylamino





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- 7. A compound according to claim 1 wherein R⁴ is -(CR¹6R¹7)<sub>m</sub>-C≡C-(CR¹6R¹7)<sub>t</sub>R9,
   30 wherein m is an integer from 0 to 3, and t is an integer from 0 to 5.
  - 8. A compound according to claim 1 wherein  $R^4$  is  $-(CR^{16}R^{17})_m$ - $C\equiv C-(CR^{16}R^{17})_tR^9$ , wherein m is an integer from 0 to 3, and t is an integer from 0 to 5, wherein  $R^9$  is selected from 3-piperidinyl and 4-piperidinyl each of which is optionally substituted with 1 or 2  $R^8$  groups.
  - 9. A compound according to claim 1 wherein R<sup>4</sup> is –(CR<sup>16</sup>R<sup>17</sup>)<sub>m</sub>-C=C-(CR<sup>16</sup>R<sup>17</sup>)<sub>t</sub>-R<sup>9</sup>, wherein m is an integer from 0 to 3, and t is an integer from 0 to 5.
    - 10. A compound according to claim 1 wherein  $R^4$  is  $-(CR^{16}R^{17})_m$ -C=C- $(CR^{16}R^{17})_t$ -R<sup>9</sup>, wherein m is an integer from 0 to 3, and t is an integer from 0 to 5, wherein R<sup>9</sup> is selected from 3-piperidinyl and 4-piperidinyl (optionally substituted with 1 or 2 R<sup>8</sup> groups).
- 11. A compound according to claim 1 wherein R⁴ is –(CR¹6R¹7)<sub>m</sub>-C≡C-(CR¹6R¹7)<sub>k</sub>R¹³,
   40 wherein k is an integer from 1 to 3 and m is an integer from 0 to 3.





12. A compound according to claim 1 wherein  $R^4$  is  $-(CR^{16}R^{17})_m$ - $C\equiv C-(CR^{16}R^{17})_kR^{13}$ , wherein k is an integer from 1 to 3 and m is an integer from 0 to 3, wherein  $R^{13}$  is  $-NR^1R^{14}$ , wherein  $R^{14}$  is selected from  $-C(O)R^{15}$ ,  $-SO_2R^{15}$ , and  $-C(O)NR^{15}R^7$ .

13. A compound according to claim 1 wherein  $R^4$  is  $-(CR^{16}R^{17})_m$ -C=C- $(CR^{16}R^{17})_k$ R<sup>13</sup>, wherein k is an integer from 1 to 3 and m is an integer from 0 to 3.

14. A compound according to claim 1 wherein  $R^4$  is  $-(CR^{16}R^{17})_m$ -C=C- $(CR^{16}R^{17})_kR^{13}$ , wherein k is an integer from 1 to 3 and m is an integer from 0 to 3, wherein  $R^{13}$  is  $-NR^1R^{14}$ , wherein  $R^{14}$  is selected from  $-C(O)R^{15}$ ,  $-SO_2R^{15}$ , and  $-C(O)NR^{15}R^7$ .

15. A compound according to claim 1 wherein  $R^4$  is  $-(CR^{16}R^{17})_m$ - $C\equiv C-(CR^{16}R^{17})_k$   $R^{13}$  or  $-(CR^{16}R^{17})_m$ - $C=C-(CR^{16}R^{17})_k$   $R^{13}$ , wherein k is an integer from 1 to 3 and m is an integer from 0 to 3,  $R^{13}$  is  $-NR^1R^{14}$  or  $-OR^{14}$ ,  $R^{14}$  is  $R^{15}$ ,  $R^{15}$  is  $R^{18}$ , and  $R^{18}$  is  $C_1$ - $C_6$  alkyl optionally substituted by  $-OR^6$ ,  $-S(O)_iR^6$ ,  $-NR^6R^7$ ,  $-NR^6C(O)R^7$ ,  $-NR^6SO_2R^7$ ,  $-NR^6CO_2R^7$ ,  $-NR^6CO_2R^7$ ,  $-NR^6CO_2R^7$ , or halo.

16. A compound according to claim 1 selected from the group consisting of:

(<u>+</u>)-[3-Methyl-4-(pyridin-3-yloxy)-phenyl]-(6-piperidin-3-ylethynyl-quinazolin-4-yl)-amine;

2-Methoxy-N-(3-{4-[3-methyl-4-(pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-acetamide

 $(\underline{+})$ -[3-Methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-(6-piperidin-3-ylethynyl-quinazolin-4-yl)-amine;

2-Methoxy-N-(3-{4-[3-methyl-4-(2-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-acetamide

[3-Methyl-4-(2-methyl-pyridin-3-yloxy)-phenyl]-(6-piperidin-4-ylethynyl-quinazolin-4-yl)-amine

[3-Methyl-4-(6-methyl-pyridin-3-yloxy)-phenyl]-(6-piperidin-4-ylethynyl-quinazolin-4-yl)-amine;

2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-acetamide;

2-Fluoro-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-acetamide;

E-2-Methoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide;

[3-Methyl-4-(pyridin-3-yloxy)-phenyl]-(6-piperidin-4-ylethynyl-quinazolin-4-yl)-amine;

2-Methoxy-N-(1-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-ylethynyl}-cyclopropyl)-acetamide;

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*E*-N-(3-{4-[3-Chloro-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-2-methoxy-acetamide;

N-(3-{4-[3-Chloro-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-acetamide;

N-(3-{4-[3-Methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-acetamide;

*E*-N-(3-{4-[3-Chloro-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide;

*E*-2-Ethoxy-N-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-acetamide;

15 1-Ethyl-3-(3-{4-[3

1-Ethyl-3-(3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-urea;

Piperazine-1-carboxylic acid (3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-amide;

(<u>+</u>)-2-Hydroxymethyl-pyrrolidine-1-carboxylic acid (3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-amide;

2-Dimethylamino-N-(3-{4-[3-methyl-4-(pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-acetamide;

*E*-N-(3-{4-[3-Methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-allyl)-methanesulfonamide;

Isoxazole-5-carboxylic acid (3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-amide;

1-(1,1-Dimethyl-3-{4-[3-methyl-4-(6-methyl-pyridin-3-yloxy)-phenylamino]-quinazolin-6-yl}-prop-2-ynyl)-3-ethyl-urea;

and the pharmaceutically acceptable salts, prodrugs and solvates of the foregoing compounds.

- 17. A method for the treatment of abnormal cell growth in a mammal comprising administering to said mammal an amount of a compound of claim 1 that is effective in treating abnormal cell growth.
  - 18 A method according to claim 17 wherein said abnormal cell growth is cancer.
- 19. A method according to claim 18 wherein said cancer is selected from lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of

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- the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system (CNS), primary CNS lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, or a combination of one or more of the foregoing cancers.
  - 20. A method for the treatment of abnormal cell growth in a mammal which comprises administering to said mammal an amount of a compound of claim 1 that is effective in treating abnormal cell growth in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, radiation, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, antibodies, cytotoxics, anti-hormones, and anti-androgens.
  - 21. A pharmaceutical composition for the treatment of abnormal cell growth in a mammal comprising an amount of a compound of claim 1 that is effective in treating abnormal cell growth, and a pharmaceutically acceptable carrier.